

## Clinical Outcome and Immune Follow-Up of Different Surgical Approaches for Human Cyst Hydatid Disease in Liver

Xinhua Chen, Xinmei Chen, Yingmei Shao, Jingming Zhao, Haitao Li, and Hao Wen\*

Department of Hepatobiliary Surgery, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; Department of Pharmacy, Shandong University of Traditional Chinese Medicine, Jinan Shandong, China; Xinjiang Key Laboratory of Echinococcosis, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, China

**Abstract.** A new surgical approach (subadventitial cystectomy) has been developed for liver hydatid disease. We retrospectively compared clinical outcomes and immune status 24 months after a subadventitial cystectomy with traditional surgical approaches. Patients with liver hydatid cysts were treated with a subadventitial cystectomy ( $N = 11$ ), pericystectomy ( $N = 16$ ), partial pericystectomy ( $N = 18$ ), or hepatic resection ( $N = 12$ ). By the end of the follow-up period, the subadventitial cystectomy group had the fewest post-operative complications and shortest hospital stays. Two recurrences occurred: one recurrence after partial pericystectomy and one recurrence after pericystectomy. The total immunoglobulin E (IgE) level decreased significantly in the subadventitial cystectomy group. The post-surgery IgG level was lower in the subadventitial cystectomy than the pericystectomy and partial pericystectomy groups. In conclusion, subadventitial cystectomy completely removes the parasite, causing lower complication rates and lower immune reactions.

### INTRODUCTION

Cystic hydatid disease is a global parasitic zoonosis caused by the larval stages of the dog tapeworm *Echinococcus granulosus*.<sup>1</sup> Humans become contaminated by ingestion of parasite eggs after close contact with infected dogs. The eggs develop into larvae when they cross the intestinal wall and migrate through the portal vein into the liver, where they grow into cysts.<sup>2</sup> Such liver cysts can be asymptomatic for years until they compress the surrounding organs. Without treatment, the cysts may form fistulas into adjacent organs or rupture into the abdomen.<sup>3</sup>

Hydatid disease has become a serious public problem in China. The results of a Chinese national survey<sup>4</sup> found that, among 239 individuals tested, 12.04% were serology-positive and 1.08% ultrasound-positive. In 2005, a survey estimated that 380,000 Chinese individuals had hydatid disease. Currently, at least 270 million people (58% of the total population) are at risk for cystic hydatid disease in central Asia and western China. The annual surgical incidence rate in Uzbekistan and Tajikistan has been estimated to be as great as 25–27 cases per 100,000, with prevalence of approximately 10% (range = 0.8–11.9%) in some Tibetan communities in western China.<sup>5</sup>

Management of hydatid disease carries a substantial risk of complications and recurrence. Chemotherapy with albendazole, percutaneous drainage, and laparoscopic, endoscopic, and open surgical approaches have all been used to manage the disease. The aim of surgery is to kill the parasites, evacuate the cyst, remove the germinal layer, and obliterate the residual cavity.<sup>6</sup> The most commonly used surgical approaches are pericystectomy, partial pericystectomy, and hepatic resection (hepatectomy or segmentectomy).<sup>7</sup> The optimal surgical approach varies according to the condition of the cyst and the patient (e.g., the general status of the patient and the cyst size, location, and pathology). The open surgeries have a substantial risk of complications (e.g., bile leakage, parasite contamination, and presence of dead spaces in which an abscess can

form).<sup>8</sup> These complications then have to be managed with more radical surgical approaches.<sup>9</sup>

Peng and others<sup>10</sup> introduced a new surgical approach for hydatid disease named subadventitial cystectomy, during which the parasitic cysts are completely removed. Peng and others<sup>10</sup> discovered that the pericyst consists of two tissue layers of different histological origin: the adventitial layer directing toward the liver parenchyma is from fibrosis and compression of the vessels of Glisson capsules and hepatic veins, and the exocyst layer directing toward the cyst of the parasite is from granulomatous reaction.<sup>11</sup> The pericyst provides a space in which the exocyst layer can easily be detached from the adventitial layer. Compared with radical hepatic resection, subadventitial cystectomy can better protect the adventitial layer adjacent to the hepatic parenchyma, resulting in less damage to healthy liver and less bleeding.<sup>12</sup> Our medical center began applying subadventitial cystectomy in 2001. Here, we report the follow-up data for clinical outcomes and immune reactions.

### METHODS

**Patients.** The records of 57 patients (31 males and 26 females) who underwent surgery at the Department of Surgery of The First Teaching Hospital of Xinjiang Medical University between January of 2001 and January of 2002 were retrospectively reviewed. The average age of the patients at the time of surgery was 45 years.

**Preoperative diagnosis and albendazole treatment.** All patients were diagnosed by ultrasonography or a combination of computerized tomography and immunological assays. They were treated with liposomal albendazole (10 mg/kg per day) for 3 weeks before the surgery and then 3 months after the surgery.

**Surgical procedure.** The procedures for subadventitial cystectomy, pericystectomy, partial pericystectomy, and radical hepatic resection were in accordance with those in *The Principles for Diagnosis and Treatment of Human Hydatid Disease* by the Ministry of Health of China. The procedures, including obtaining informed consent, were conducted in accordance with the Ethical Committee on Human Experimentation of Xinjiang Medical University. The surgical procedures are illustrated in Figures 1–3, and the key steps are described. Briefly, hepatic resection was performed using an anatomical approach based on Couinaud's classification (Figure 3).

\* Address correspondence to Hao Wen, State Key Laboratory Incubation Base of Xinjiang Major Diseases Research (2010DS890298) and Xinjiang Key Laboratory of Echinococcosis, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang 830054, China. E-mail: wenhao@superinfo.info

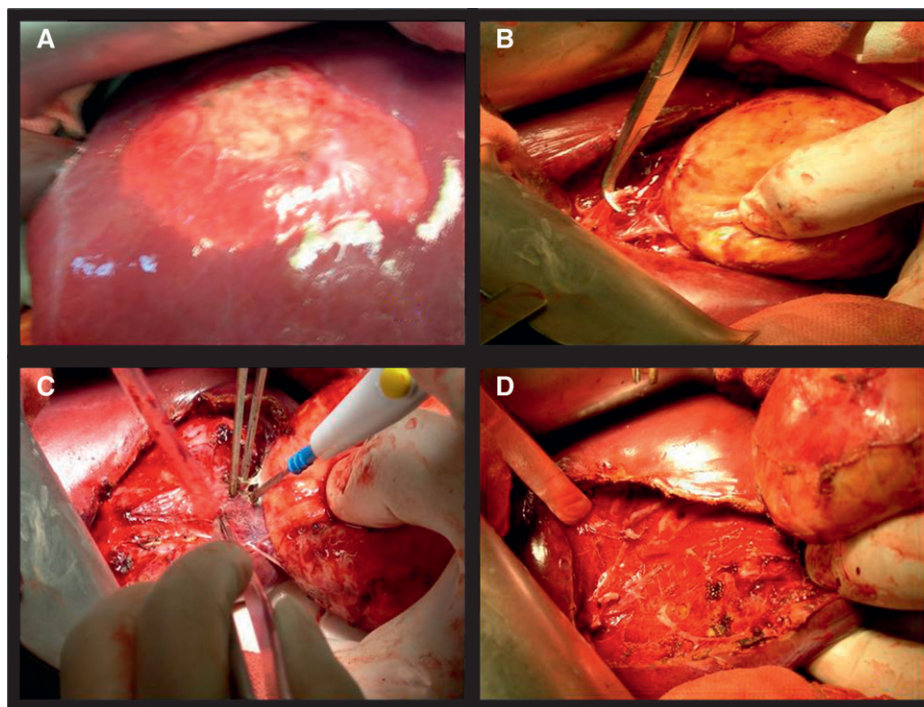


FIGURE 1. Subadventitial cystectomy. (A) The first step is to locate the cyst. Several gauze clothes saturated with hypertonic saline are introduced into the abdominal cavity and placed around the cyst to protect against hydatid fluid leakage. (B) The second step is to look for the space between the normal hepatic parenchyma and the pericyst. The first incision is made through the healthy live parenchyma just adjacent to the pericyst. The pericyst is the pseudoanatomical layer of the host surrounding the parasite, and the pericyst has different layers. After hemostasis is achieved, an attempt is made to look for any biliary leakage. The bile ducts are then either clipped or ligated and divided. With blunt dissection, the pericyst is separated from the hepatic tissue. The key to subadventitial cystectomy is to leave the laminated membrane on the pericyst (i.e., the liver tissue) while separating it from the compressed host tissue. (C) During blunt dissection, vascular and bile ducts  $> 3$  mm are clipped. (D) After completion of the subadventitial pericystectomy, the cyst will be totally separated from the liver, and the smooth surface of the liver parenchyma is examined for bleeding and bile leakage.

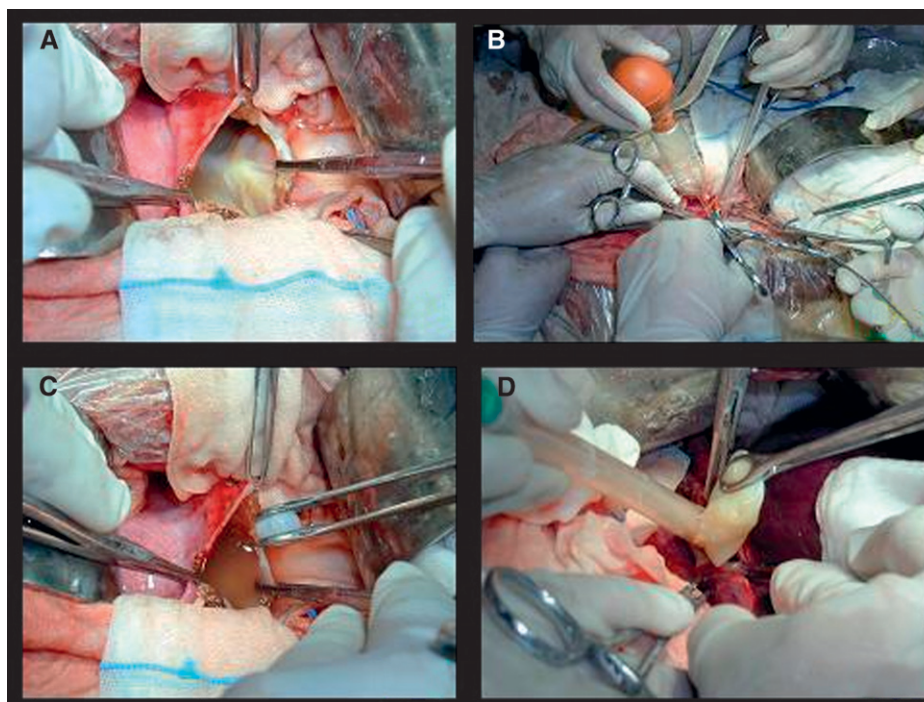


FIGURE 2. Total or partial pericystectomy. (A) The cyst is opened after the cyst fluid had been aspirated with a 20-gauge needle syringe to reduce the pressure. (B) Suction apparatus is inserted into the cyst for complete aspiration of the cyst fluid. (C) Daughter cysts are removed from the open cyst. (D) The visible daughter cysts are removed, and the residue cyst is flushed with hypertonic saline solution for 10 minutes before it is closed with a drainage tube left inside.



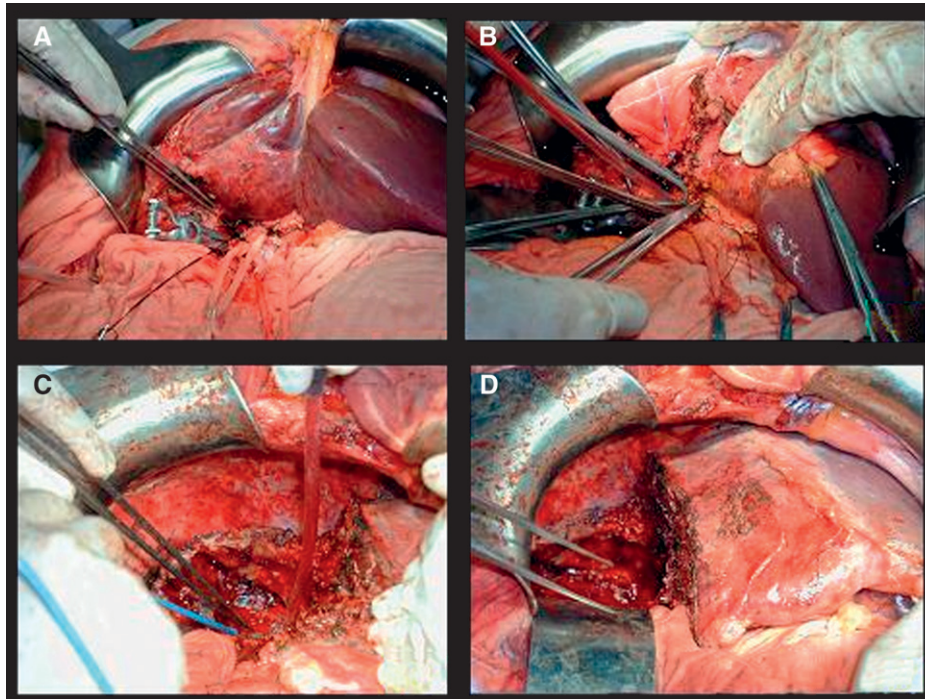


FIGURE 3. Hepatic resection. (A) Parasite cysts occupying a major part of a liver lobe (in this case, the right lobe). (B) The main vessels are separated from each other. (C) The right lobe is removed along with the cyst. (D) A drainage tube is placed to control liver bleeding.

Pericystectomy and partial pericystectomy (Figure 2) were performed in patients with bilateral liver involvement or portal vein/inferior vena cava involvement. In these procedures, the cyst roof was opened, and then, the cyst fluid and contents were evacuated by negative pressure suction. The residual cavity was rinsed by hypertonic saline and then drained to prevent abscess or bilioma. In subadventitial cystectomy, the small gap between the liver parenchyma and the outer membrane of the cyst was separated from and completely peeled off the cyst by enucleation (Figure 1).

**Post-surgery follow-up.** Patients were evaluated routinely before surgery, at monthly intervals during the first 1 year after surgery, and then, annually; serodiagnosis, immunoglobulin (Ig), and ultrasonography were tested at each evaluation. The concentrations of total IgM, IgE, and IgG were determined by a nephelometric technique (Beckman Array 360; Beckman Coulter Instruments, Brea, CA). The concentration of the specific IgG against cyst fluid antigens was determined by enzyme-linked immunosorbent assay (ELISA). Antigen cystic fluid (CF) was the diagnostic antigen extracted from crude E.

## RESULTS

The clinical outcomes of 57 patients are summarized in Table 1. No post-operative complications were recorded in the subadventitial cystectomy group; one complication was recorded in the pericystectomy group, three complications were recorded in the partial pericystectomy group, and two complications were recorded in the radical liver resection group. The subadventitial cystectomy group also had the shortest hospital stays. During follow-up, a cyst recurrence occurred in two patients in the partial pericystectomy group and one patient in the pericystectomy group.

The total IgM level decreased immediately after surgery and then increased 1 month after surgery. It finally decreased to a normal level in all four groups and was not significantly different than that in healthy controls (Figure 4). In all four groups, the total IgE level had decreased to a normal level by 12 months after surgery (Figure 5). The total IgE level decreased more rapidly in the two radical surgery groups than in the subadventitial cystectomy and radical hepatic resection groups. The total IgG level decreased gradually in all four groups (Figure 6), and the level of the specific IgG against cyst fluid antigens also decreased (Figure 7). Twelve months after surgery, the level of the specific IgG against cyst fluid antigens was significantly elevated in the pericystectomy and partial pericystectomy groups but nearly normal in the subadventitial cystectomy and the hepatic resection groups (Figure 7).

TABLE 1  
Clinical outcomes of patients treated with different surgical approaches

	Subadventitial cystectomy	Pericystectomy	Partial pericystectomy	Hepatic resection
Number of patients	11	16	18	12
Mean age (years)	39	38	38	39
Sex (male/female)	5/6	7/9	8/10	6/6
Total number of cysts	19	22	21	20
Mean cyst size (cm)	10	12	14	11
Positive serodiagnosis	11/11	15/16	16/18	12/12
Blood loss (mL)	70	—	—	280
Operation time (minutes)	90	50	40	120
Number of complications	0	1	2	3
Length of hospital stay (days)	7.4	7.9	8.5	12.8
Recurrence	0	1	2	3

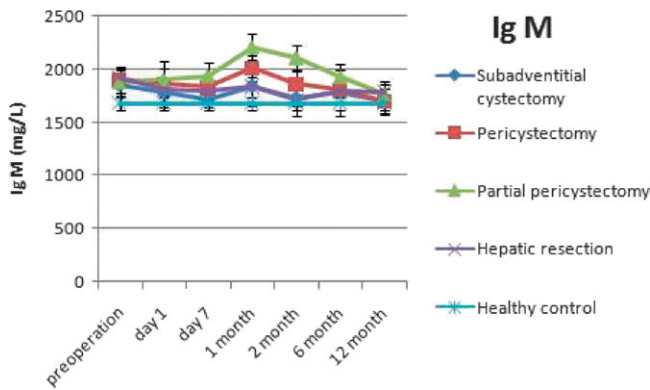


FIGURE 4. Total IgM before and after surgery. Patients were routinely evaluated by serodiagnosis. The total IgM level was determined using a nephelometric technique. For all four groups, the total IgM decreased slightly after the surgery and then increased 1 month after surgery before falling to a normal level. The final level was similar to that for healthy controls ( $P > 0.05$ ).

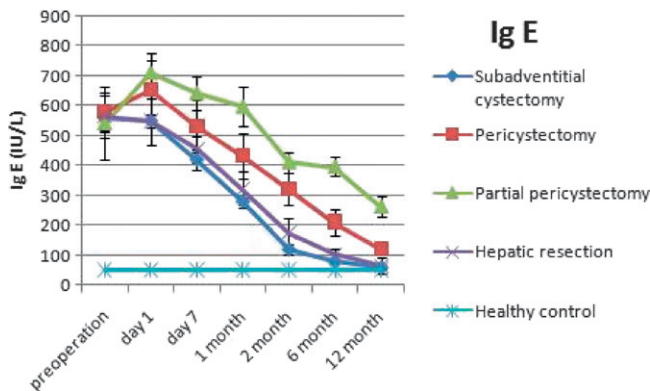


FIGURE 5. Total IgE levels before and after surgery. Patients were routinely evaluated by serodiagnosis. The total IgE level was determined using a nephelometric technique. For all groups, the total IgE peaked 1 day after surgery and then decreased to a normal level 6 months after surgery.

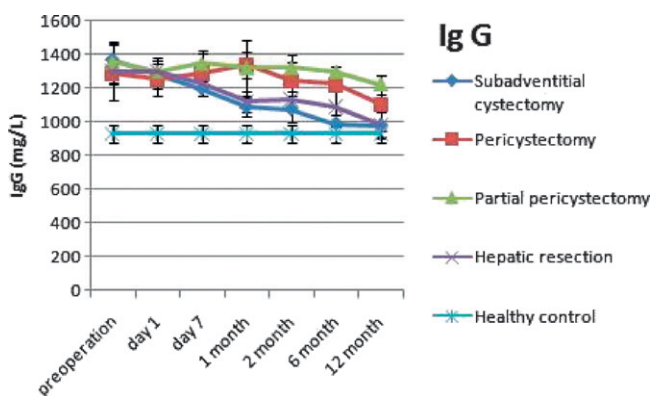


FIGURE 6. Total IgG before and after surgery. Patients were routinely evaluated by serodiagnosis. The total IgG level was determined using a nephelometric technique with Array System 360 by Beckman Coulter. Total IgG decreased gradually in all four groups. The IgG levels were significantly different at the end of the follow-up period.

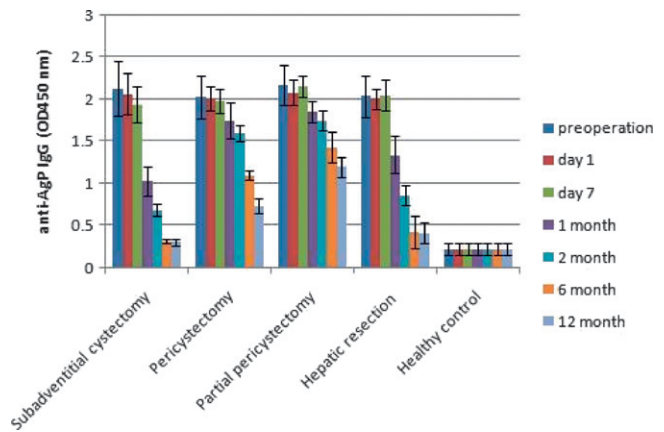


FIGURE 7. The level of the specific IgG against cyst fluid antigens before and after surgery. The level of the specific IgG against cyst fluid antigens was tested using ELISA. The level decreased after surgery in all four groups but at different rates. Twelve months after surgery, the specific IgG level against cyst fluid was still significantly higher than baseline in the pericystectomy and partial pericystectomy groups but had decreased to a normal level in the subadventitial cystectomy and hepatic resection groups. AgP = antigen protoscolices; OD = optical density.

## DISCUSSION

Traditionally, a hydatid cyst has been considered to be composed of an outer layer of inflammatory tissue and an inner germinal membrane,<sup>13</sup> which is the anatomical and histological basis for pericystectomy and partial pericystectomy; during these procedures, the fibrous capsule is cut open to allow the cyst fluid, daughter cysts, and germinal layer to be removed.<sup>14</sup> However, cutting the cyst open increases the risk of the parasite spreading, and the residue capsule is a potential hazard for post-surgical abscess formation.<sup>15</sup>

The parasite evokes an immune response that is involved in the formation of an adventitious capsule.<sup>12</sup> In surgery, the parasite cyst can be found as fibrous capsules. The histology origin of fibrous capsules in parasite and host sides is different.

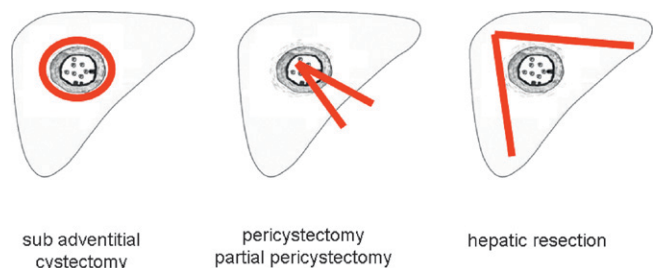


FIGURE 8. Illustration of a hydatid cyst and the separation focus in the four different surgeries. The pericyst consists of two layers of different histological origin: the adventitial layer directing toward the liver parenchyma is caused by fibrosis and compression of vessels of Glisson capsules and hepatic veins, and the exocyst layer directing toward the parasite cyst is caused by granulomatous reaction. The pericyst provides a space in which the exocyst layer can easily be detached from the adventitial layer. When the abdomen is opened to expose the cyst, a dense outermost cyst layer and a fibrous protective zone of host origin are seen. The latter is the compressed liver parenchyma and fibrous tissue that had been formed by the expanding cyst. Underneath these layers is a compressed laminated membrane that is acellular and allows nutrient to pass into the cyst interior. The innermost layer of the cyst is a germinal layer, where the protoscolices is produced. Daughter vesicles are shown as small spheres that contain the protoscolices.

Granuloma-like pathologic changes have been reported near the parasite, and depressed Glisson capsules and a depressed hepatic vein system have been found near the host. The inflammatory infiltration in the fibrous portal tracts around the cyst and the fibrous capsule contains monocytes, lymphocytes, and eosinophils. The presence of an intense inflammatory infiltration in the liver parenchyma surrounding hydatid cysts causes hepatocyte derangements and stimulates fibrogenesis. The parasite has only a laminated membrane containing protoscolices, which forms connective tissue septa in the periportal zone.

This discovery changed the view of the space that exists between the inner capsule of the parasite cyst and the outer thin layer of the capsule formed by the host, indicating that there may be a space between the liver parenchyma and outer membrane of the cyst. Consequently, a new surgical approach named subadventitial cystectomy was developed on the basis of these observations. Subadventitial cystectomy is a radical treatment that removes the whole cyst while retaining the largest amount of healthy liver tissue. Subadventitial cystectomy is illustrated in Figure 8 along with the traditional surgical approaches.

Immunological follow-up showed that all surgeries reduced the parasite burden, resulting in a decrease in the total IgE level. The parasite infection was resolved most quickly and most completely after subadventitial cystectomy. In all four groups, the total IgG level was greater than normal before the surgery and decreased to within the normal range within 1 year. However, the level of the specific IgG antibody against the hydatid cyst fluid antigens decreased within the normal range by 6 months in the subadventitial cystectomy and hepatic resection groups. The level of the specific IgG antibody in the pericystectomy or partial pericystectomy groups remains high even 1 year after surgery, indicating that only the radical surgical approaches, such as subadventitial cystectomy and hepatic resection, can thoroughly remove the parasite.

Clinical outcomes indicate that pericystectomy and partial pericystectomy are easy to perform and associated with minimal blood loss and operation time. However, the rate of recurrence of cysts was significantly greater than in subadventitial cystectomy and hepatic resection. The hepatic resection took longer time to perform and was associated with more blood loss but caused a low rate of cyst recurrence. Subadventitial cystectomy caused less damage to healthy liver tissue than hepatic resection.

Although subadventitial cystectomy has many advantages, it requires a critical skill to identify the small gap between the liver parenchyma and the outer membrane of the parasite cyst. Failure to accurately identify this gap will cause hepatic parenchyma hemorrhage that will blur the surgical field and increase the difficulty of further separation. This approach is not suitable for patients with cysts near the vital vessels or bile ducts. No matter which surgical approach is chosen, active management of the residual cavity must be taken to prevent biliary leakage, biliary fistula, and abscesses. Surgeons must decide on the appropriate solution (e.g., omentoplasty or tube drainage) according to the size and location of the cyst and the existence of complications.

## CONCLUSIONS

Each surgical approach has its advantages and disadvantages, and no approach is suitable for all cysts. However, complete resection of hepatic hydatid cysts should be per-

formed whenever possible. Our results suggest that, with the right indication, subadventitial cystectomy has low post-operative complication, mortality, and recurrence.

Received March 23, 2014. Accepted for publication June 24, 2014.

Published online July 28, 2014.

Acknowledgments: All authors thank Dr. Xinyu Peng from Shihezi University for his training with this skill of subadventitial cystectomy.

Financial support: This research is supported by National Natural Science Foundation of China Grants 81372425 and U1303222, Program for Changjiang Scholars and Innovative Research Team in Universities IRT1181, Zhejiang Medical Research Funding Grant LY13H180003, and Xinjiang Science and Technology Bureau Project 2013911131.

Authors' addresses: Xinhua Chen, Department of Hepatobiliary Surgery, The First Affiliated Hospital of Zhejiang University, Hangzhou, China, E-mail: xinhua\_chen@zju.edu.cn. Xinmei Chen, Department of Pharmacy, Shandong University of Traditional Chinese Medicine, Jinan, China, E-mail: xinmeichen@126.com. Yinmei Shao, Jingming Zhao, Haitao Li, and Hao Wen, Department of Surgery, Xinjiang Medical University, Urumqi, China, E-mails: syingmei3000@163.com, zixiu123@sina.com, lht45182@163.com, and Dr.wenhao@163.com.

## REFERENCES

- Caremani M, Benci A, Maestrini R, Rossi G, Menchetti D, 2006. Abdominal cystic hydatid disease (CHD): classification of sonographic appearance and response to treatment. *J Clin Ultrasound* 24: 491–500.
- Voros D, Katsarelis D, Polymeneas G, Polydorou A, Pistiolis L, Kalovidouris A, Gouliamos A, 2007. Treatment of hydatid liver disease. *Surg Infect (Larchmt)* 8: 621–627.
- Safioleas MC, Misiakos EP, Kouvaraki M, Stamatakis MK, Manti CP, Felekouras ES, 2006. Hydatid disease of the liver: a continuing surgical problem. *Arch Surg* 141: 1101–1108.
- Qi Zheng, Samantha Vanderslott, Bin Jiang, LiLi Xu, Cong-Shan Liu, LeLe Huo, LiPing Duan, NingBo Wu, ShiZhu Li, ZhiGui Xia, WeiPing Wu, Wei Hu, Hao-Bing Zhang, 2013. Research gaps for three main tropical diseases in the People's Republic of China. *Infectious Diseases of Poverty* 2: 15.
- Zhang W, Zhang Z, Wu W, Shi B, Li J, Zhou X, Wen H, McManus DP, 2014. Epidemiology and control of echinococcosis in central Asia, with particular reference to the People's Republic of China. *Acta Trop*. doi:10.1016/j.actatropica.2014.03.014.
- Junghanss T, da Silva AM, Horton J, Chiodini PL, Brunetti E, 2008. Clinical management of cystic echinococcosis: state of the art, problems, and perspectives. *Am J Trop Med Hyg* 79: 301–311.
- Smego RA Jr, Sebanego P, 2005. Treatment options for hepatic cystic echinococcosis. *Int J Infect Dis* 9: 69–76.
- Prousalidis J, Kosmidis C, Fahantidis E, Harlaftis N, Aletras O, 2004. Surgical treatment of multiple cystic echinococcosis. *HPB (Oxford)* 6: 110–114.
- Vuitton DA, Wen H, 2007. Treatment of cystic echinococcosis: a combination of general goals and rules, individual decisions and indications. *Neth J Med* 65: 86–88.
- Peng X, Li J, Wu X, Zhang S, Niu J, Chen X, Yao J, Sun H, 2006. Detection of Osteopontin in the pericyst of human hepatic *Echinococcus granulosus*. *Acta Trop* 100: 163–171.
- da Silva AM, 2010. Human echinococcosis: a neglected disease. *Gastroenterol Res Pract* 2010: 583297.
- Da Silva AM, 2011. Hydatid cyst/cystic echinococcosis: anatomical and surgical nomenclature and method to quantify the cyst content solidification. *Chin Med J (Engl)* 124: 2806–2812.
- Hoda SA, Hoda RS, 2002. Images in pathology: intraoperative cytology of hydatid cyst. *Int J Surg Pathol* 10: 209.
- El Malki HO, Souadka A, El Mejdoubi Y, Zakri B, Benkabbou A, Mohsine R, Ifrine L, Belkouchi A, 2007. Surgery in intra-abdominal ruptured hydatid cyst. *World J Surg* 31: 1525.
- Aydin U, Yazici P, Onen Z, Ozsoy M, Zeytinlu M, Kiliç M, Coker A, 2008. The optimal treatment of hydatid cyst of the liver: radical surgery with a significant reduced risk of recurrence. *Turk J Gastroenterol* 19: 33–39.